CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215256Orig1s000

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

IND 126360

MEETING MINUTES

Novo Nordisk Inc.
Attention: Stephanie DeChiaro
Director, Regulatory Affairs
P.O. Box 846
800 Scudders Mill Rd.
Plainsboro, NJ 08536

Dear Ms. DeChiaro:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for semaglutide injection.

We also refer to the telecon between representatives of your firm and the FDA on August 11, 2020. The purpose of the meeting was to discuss filing and format issues related to the submission of the NDA for semaglutide 2.4 mg (once weekly) for weight management.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Patricia Madara, Regulatory Project Manager, at 301-796-1249.

Sincerely,

{See appended electronic signature page}

John M. Sharretts, MD
Deputy Director (Acting)
Division of Diabetes, Lipid Disorders and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: PreNDA

Meeting Date and Time: August 11, 2020 at 10:30 AM – 11:30 AM eastern time
Meeting Location: teleconference

Application Number: IND 126360
Product Name: semaglutide injection; 2.4 mg
Indication: chronic weight management
Sponsor Name: Novo Nordisk
Regulatory Pathway: 505(b)(1)

Meeting Chair: John Sharretts, MD
Meeting Recorder: Patricia Madara, MS

FDA Attendees

Office of New Drugs (OND); Office of Cardiology, Hematology, Endocrinology and Neurology (OCHEN):

Ilan Irony, MD	Deputy Director (Acting)

OND; OCHEN; Division of Diabetes, Lipid Disorders and Obesity (DDLO)

Lisa Yanoff, MD	Director (Acting)
John Sharretts, MD	Deputy Director (Acting)
Julie Golden, MD	Medical Officer
Patricia Madara, MS	Regulatory Project Manager

OND; OCHEN; Division of Pharmacology / Toxicology for DDLO

Federica Basso, PhD	Team Leader
Elena Braithwaite, PhD	Pharmacology/Toxicology Reviewer

Office of Translational Sciences (OTS); Office of Biostatistics; Division of Biometrics II

Feng Li, PhD	Team Leader
Kiya Hamilton, PhD	Statistical Reviewer

OTS; Office of Clinical Pharmacology (OC); Division of Cardiometabolic and Endocrine Pharmacology (DCEP)

Jaya Vaidyanathan, PhD	Team Leader
LaiMing Lee, PhD	Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality (OPQ); New Drug Products Branch 5

Muthukumar Ramaswamy, PhD Quality Assessment Lead

Office of Surveillance and Epidemiology (OSE)

Nichelle E. Rashid	Lead Reg Health Project Manager
Terrolyn Thomas, MS, MBA	Senior Reg Health Project Manager

OSE; Office Of Medication Error Prevention And Risk Management (DMEPRM); Division of Medication Error Prevention (DMEPA)

Ariane Conrad, PharmD, BCACP, CDCES, FISMP Safety Evaluator

Office of Compliance; Office of Scientific Investigations; Division of Clinical Compliance Evaluation; Good Clinical Practice Assessment Branch

Cynthia Kleppinger, MD Senior Medical Officer

Center for Device Evaluation and Radiological Health; Office of Product Evaluation and Quality (OPEQ); Office of Health Technology III; Division of Health Technology 3 C (Drug Delivery and General Hospital Devices and Human Factors)

Rong Guo, PhD Device reviewer

SPONSOR ATTENDEES

Anders Nørby,	Project Vice President, New Platform Design
Anne Phillips,	Senior Vice President, US Clinical, Medical and Regulatory Affairs
Bettina Svanholm Flensted,	Regulatory Professional, HQ Regulatory Affairs
Bjarke Dupont Jørgensen,	System Engineer Specialist, New Platform Design
Bryan Goldman,	Principal Statistician, Biostatistics Obesity and Metabolism
Bjørg Hunter,	Department Manager Devices, HQ Regulatory Affairs
Devraj Chakravarty,	Senior Manager, US Regulatory Affairs
Divya Menon Andersen,	Senior Global Regulatory Lead, HQ Regulatory Affairs
Elisabeth Børresen Elmqvist,	CMC Project Director, Peptides & Small Molecules
Lisbeth Vesterg. Jacobsen,	Senior Clinical Pharmacology Advisor, Clinical Pharmacology Obesity
Marianne ØlholmLarsenGrønning,	Corporate Project Vice President, Obesity and Metabolism

Mette Thomsen,	Senior Director, Medical & Science Obesity & Metabolism
Marie Lindegaard,	Project Vice President, Obesity and Metabolism
Marie Thi Dao Tran,	Senior International Medical Manager, Medical & Science Obesity & Metabolism
Robert Clark,	Vice President, US Regulatory Affairs
Signe Zaar Grønlund,	Senior Regulatory Professional, HQ Regulatory Affairs
Stephanie DeChiaro,	Senior Director, US Regulatory Affairs
Toni Auene Tuxen,	Statistical Programming Specialist, Biostatistics Obesity and Metabolism

1.0 Background

Semaglutide (NN9536) is a long-acting GLP-1 receptor agonist originally studied as an adjunct to diet and exercise for the treatment of type 2 diabetes mellitus (T2D). That development program is completed and semaglutide injection for T2D is approved under NDA 209637 (Ozempic).

Under IND 126360, semaglutide injection is being developed for chronic weight management at a higher dose (2.4 mg once weekly). There are currently four ongoing or completed phase 3 trials that will be included in the NDA submission. In addition, the results from a phase 2 dose-finding study and several phase 1 trials will be submitted. The purpose of this Type B meeting is to discuss and agree on the NDA content and format and to identify any issues that could delay submission or result in a refuse-to-file decision. To aid in their understanding of the NDA requirements, the sponsor has included clinical (safety, efficacy, statistical, patient reported outcomes and immunogenicity) and regulatory questions for FDA.

FDA sent Preliminary Comments to NovoNordisk on August 6, 2020.

2.0 Discussion

After review of the preliminary comments, the sponsor requested additional discussion of Question #13 (CMC and device comments) and “Additional FDA Comment” #6 (laboratory values in narratives). There was no additional discussion of any other sponsor Questions or FDA Comments.

2.1. Clinical

Questions 1 and 2

The proposed cut-off date for data to be included in the NDA is 11 November 2020, corresponding to the date of database lock for trial 4590, which is the final trial to be included in the NDA.

This cut-off date will allow inclusion of data from the 8 completed clinical trials with semaglutide s.c. (4 phase 3a trials, 1 phase 2 trial and 3 clinical pharmacology trials).

The phase 3a trials alone constitute a total of at least 4500 randomised subjects, of whom approximately 3000 subjects will have been exposed to semaglutide s.c. (see Table 8-1 for details on trials to be included in the NDA).

The overall analysis of safety data, safety methodology and the pooling strategy for the upcoming NDA submission was agreed with FDA at a Type C meeting (written feedback) on 18 September 2019. For further information on the statistical analysis plan for the Integrated Summary of Safety (ISS), see ISS SAP submitted to the IND 126360 (serial no. 0486) on 16 April 2020.

The NDA will include blinded safety data (deaths, serious adverse events and pregnancies) from 6 ongoing trials. Ongoing is defined as a trial that has had first patient first visit but has not yet had database lock at the time of the proposed NDA cut-off date. For further information on the randomised subjects in the ongoing trials, see *Clinical Supporting Documentation*, Table 1-1.

Does the Agency agree with the proposed cut-off for safety data in the NDA?

Does the Agency agree with the proposal for inclusion of safety data from the ongoing trials?

FDA Pre-Meeting Response

Yes, we agree with your proposals. In general, we do not consider blinded safety data to be very informative for assessing safety. If there are concerns regarding individual events, we may ask for unblinding of select reports.

Question 3

In the NDA, the efficacy of semaglutide 2.4 mg will be evaluated based primarily on the STEP 1–4 phase 3a trials; the full evaluation will be presented in the Summary of Clinical Efficacy (SCE). A brief summary of the intended approach for the evaluation is presented below. For further details see the statistical analyses plan for the SCE in the ISE SAP submitted to the IND 126360 on 16 April 2020.

The primary endpoints in all phase 3a trials except STEP 4 are percent change in body weight from baseline to week 68 and the proportion of subjects achieving body weight reduction ≥5% from baseline to week 68. In STEP 4, the primary endpoint is percent change in body weight from baseline to week 68, where baseline is defined as the time of randomisation at week 20. Other efficacy endpoints are used to further substantiate the effect of semaglutide 2.4 mg on other weight-related parameters, on cardiovascular risk factors, on glucose metabolism, and on patient-reported outcomes. The testing hierarchies showing all confirmatory endpoints for the 4 STEP phase 3a trials are listed in the ISE SAP submitted to the IND 126360 (serial no. 0486) on 16 April 2020.

In the SCE, an efficacy evaluation including the planned subgroup analyses for percent body weight change will be presented trial-by-trial (Clinical Supporting Documentation, Section 3.2). No pooling of data is planned.

The SCE text will serve as the Integrated Summary of Effectiveness (ISE) text because it is expected that a coherent analysis and presentation of the efficacy results can be

contained within the space constraints of the SCE. The SCE will adhere to the ICH M4E guidance8 and to the recommendations of the ISE guideline.

Estimands

The efficacy-related endpoints are evaluated for two pre-specified estimands (treatment policy estimand and hypothetical estimand), which are used to address the trial objectives in terms of two different aspects of the treatment effect of semaglutide 2.4 mg. All efficacy evaluations are based on data from subjects in the full analysis set (FAS).

As recommended by the Agency, the treatment policy estimand is the protocol-defined primary estimand in all global phase 3a trials, as well as in the phase 2 trial. The estimands are further introduced in Clinical Supporting Documentation, Section 4.1.1.1. The 'treatment policy' and 'hypothetical' terms are based on the draft ICH E9 addendum terminology.

Use of estimands in the New Drug Application

Novo Nordisk intends to base any superiority claims on conclusions based on the treatment policy estimand.

In the NDA, Novo Nordisk intends to base the evaluation of the clinical efficacy of semaglutide 2.4 mg on both estimands. For all endpoints, results for each estimand will be available in the SCE and/or the clinical trial reports. For all phase 3a trials (STEP 1–4), the primary estimand is the treatment policy estimand, and the analyses of the confirmatory endpoints are controlled for multiplicity only for the primary estimand. For more information on the use of estimands in the NDA, see Clinical Supporting Documentation, Section 4.1.1.2.

Statistical analyses including sensitivity analyses

Details on the applied statistical analyses and sensitivity analyses are available in Clinical Supporting Documentation, Section 4.1.1. Briefly, for continuous efficacy endpoints, the treatment policy estimand is estimated by applying an ANCOVA with multiple imputation using retrieved dropouts, and the hypothetical estimand is estimated using a mixed model for repeated measurements (MMRM). For binary endpoints, a logistic regression model is applied. For the confirmatory endpoints, appropriate sensitivity analyses, including alternate imputation strategies and tipping-point analyses, are used to assess the robustness of the conclusions to the impact of missing data.

Efficacy-related subgroup analyses

In the SCE, efficacy-related subgroup analyses will be included to assess the applicability of the benefits of semaglutide 2.4 mg in the broad population of patients with overweight or obesity. Multiple subgroups of clinical and regulatory relevance are proposed, comprising relevant demographic factors, baseline disease factors and geographical regions. The subgroup analyses will be performed for the treatment policy estimand only.

No pooling of data across trials will be done for the efficacy-related subgroup analyses because of the heterogeneity of the trial populations and designs, which would be expected to confound the interpretation of the subgroup analyses.

The efficacy-related subgroup analyses will be made on the primary endpoint and the results provided in the SCE will in general be presented as descriptive statistics and estimated treatment differences (semaglutide 2.4 mg vs placebo) by subgroup, in addition to interaction p-values. Subgroup findings will be presented in both graphical (forest plot) and tabular format. The SCE will conclude on the overall pattern across trials to help avoid basing any conclusions on potentially spurious single-trial findings, the risk of which may be greater when subgroups are small.

Note that for the 'Region' subgroup, Novo Nordisk intends to group United States and Canada in the 'North America' category. In addition, a separate report describing results in subgroups defined by patients from US/non-US sites will be created. The current number of randomized subjects for region North America is 2165, of whom 2047 subjects are from the United States and 118 subjects are from Canada. Novo Nordisk will also provide a rationale for assuming the applicability of foreign data to the US population/practice of medicine.

In addition to the summary provided above, further information and data are provided in Clinical Supporting Documentation, Section 4 and in the ISE SAP submitted to the IND 126360 (serial no. 0486) on 16 April 2020 to aid the Agency in answering the following question.

Does the Agency agree that the pre-specified analyses are adequate to establish effect and describe the effect size for semaglutide 2.4 mg in weight management?

FDA Pre-Meeting Response

Your pre-specified analyses appear acceptable.

Additional comment: Based on the results you provided, it appears the placebo arm of STEP 2 achieved higher weight loss than has been reported in other trials in patients with type 2 diabetes. Please address this observation in the SCE.

Question 4

Novo Nordisk will submit a 120-day safety update with cut-off date approximately 2 months after the NDA submission. The 120-day safety update will include blinded data from the 6 ongoing phase 3 trials and will include an estimated ~6,000 additional exposure years in ~19,000 subjects. The information provided from these trials will be for deaths, serious adverse events and pregnancies. The 120-day safety update will also include updated outcome information for any pregnancies reported as part of the NDA.

Does the Agency agree with the proposal for the 120-day safety update?

FDA Pre-Meeting Response

Yes, we agree. See the responses to Questions 1 and 2.

Question 5

(b) (4)
(b) (4), Novo Nordisk has included confirmatory secondary efficacy endpoints in the phase 3a program based on the Short Form Health Survey version 2 (SF-36v2®) Physical Functioning subscale (STEP 1–4) and Impact of Weight on Quality of Life Clinical Trials (IWQOL-Lite-CT) Physical Function composite (STEP 1–2). The efficacy endpoints related to patient reported outcomes (PROs) are presented in the Clinical Supporting Documentation, Table 4-2.

Background documentation for the IWQOL-Lite-CT Physical Function composite and the SF-36 Physical Functioning subscale will be included in the NDA (b) (4)
(b) (4)

Novo Nordisk has had the following interactions with the FDA related to clinical outcomes assessments (COAs):

- 26 October 2017: Type C meeting, FDA agreements and discussions on COA proposed for inclusion in the phase 3 studies.
- 25 June 2018: FDA advice letter on the proposed psychometric analysis plans for Weight Related Signs and Symptoms Measures (WRSSM) in obese patients with or without T2D and Impact of Weight on Quality of Life Clinical Trials version (IWQOL-Lite CT) in overweight and obese patients with T2D.
- 07 January 2019: FDA advice and information requests related to use of the IWQOL-Lite CT and the Short Form Health Survey version 2 (SF-36v2®).
- 12 August 2019 and 08 January 2020: FDA advice and information requests related to the responder definition of SF-36v2.

(b) (4)

FDA Pre-Meeting Response

In principle, the described information appears to be reasonable for review of your NDA. Plan to compile this information into an evidence dossier. We may have additional information requests during our review.

(b) (4)

[redacted]

Question 6

Novo Nordisk has followed the guidances provided by FDA and EMA on how to handle changes to trials related to COVID-19.

When the COVID-19 pandemic hit worldwide, the STEP 1–4 trials were close to last patient last treatment. This has reduced the number of subjects affected and thus the contingency measures needed. To mitigate the COVID-19 impact on the STEP trials included in the upcoming NDA, Novo Nordisk reminded the sites to use the option of converting the end-of-treatment and end-of-trial visits to phone visits if needed. It is in accordance with the protocols that the visits can be converted to phone calls in case subjects are not able to attend the clinic, to ensure safety follow-up and collection of AEs. Approximately 1% of all end-of-treatment visits have been converted to phone calls in the STEP 1 and STEP 2 trials. In the STEP 3 and STEP 4 trials all end- of-treatment visits have been performed as clinic visits, ensuring primary endpoint assessment (body weight). No changes were made to the statistical analysis plans due to COVID-19. For the STEP 1 and STEP 2 trials, the change in procedures influences the number of antibody samples and associated PK samples collected at the end-of-trial visits.

Subjects were allowed to perform a number of assessments themselves, if possible. However, in most cases, self-measurements were not performed. None of the self-measured assessments were included in any statistical analyses.

Changes to trial conduct that are related to COVID-19 will be recorded as follows and included in the clinical trial reports:

- Assessments which were self-measured by the subjects will be flagged in the datasets.
- Important PDs:
  - All PDs related to site-visits converted to phone visits due to COVID-19 will be categorised as important PDs. The PDs will be either subject-level or site-level. The site-level PDs will list the affected subjects by subject number. The

(b) (4)

[redacted]

deviations, and any impact of these on efficacy and safety results, will be summarised and discussed in the individual clinical trial reports.

Does the Agency agree that the above information that will be provided in the clinical trial reports are adequate to address the potential impact of COVID-19 on the clinical trials?

FDA Pre-Meeting Response

You should clearly identify those subjects who were impacted by COVID-19 and indicate those missing data solely due to COVID-19. In addition to the information you plan to provide in the STEP clinical trial reports, provide an overall COVID-19 summary that addresses its impact on the clinical program in Section 2.5 – Clinical Overview. For each affected trial, we suggest you include the following information or similar (as relevant to your clinical program):

Events related to COVID-19	Semaglutide dose 1 N= n (%)	Semaglutide dose 2 N= n (%)	Placebo N= n (%)
Discontinuation of treatment			
Individual level			
Site level			
Supply disruption			
Withdrawal from trial			
Individual level			
Site level (e.g., site closure)			
COVID-19 positive			
Hospitalized			
Treatment for COVID-19 – e.g., medication 1			
Treatment for COVID-19 – e.g., medication 2			
Missed primary endpoint ascertainment			
Individual level			
Site level			
Missed key secondary endpoint ascertainment			
Individual level			
Site level			
Use of alternative endpoint ascertainment			
Remote visit			
Out-of-window			

Question 7

The validated assays used in the phase 3 trials for assessment of neutralizing antibodies towards semaglutide and native GLP-1 are similar to the assays used in earlier approved semaglutide programmes (Ozempic®, NDA 209637; Rybelsus®, NDA 213051). For those programs, the Agency issued Post Marketing Commitments (PMC) aiming to improve the sensitivity of the neutralisation assays. Novo Nordisk worked with the Agency to resolve the PMCs and were released from the PMCs in September 2019 as the Agency considered the re-validated assays did “not have the capacity to assess

the neutralizing and cross-neutralizing capacity of antibodies present in the proposed samples".

Novo Nordisk has continued activities to further improve the sensitivity of the neutralizing antibody assays, and has recently identified a new control antibody, which will likely document improved sensitivity of the re-validated assays. In in-house experiments, the new control antibody appears to improve the sensitivity 3-fold for the semaglutide nAb assay and 4-fold for the native GLP-1 nAb assay in samples with low levels of semaglutide (corresponding to samples from follow-up visits). To document the sensitivity of the re-validated nAb assays, Novo Nordisk intends to include supplementary validation data with the new positive control antibody in the NDA (Integrated Summary of Immunogenicity).

At the End of Phase 2 meeting held 23 October 2017, the Agency requested evaluation of neutralizing capacity of antibodies in samples taken both during treatment and at follow-up visits after end of treatment in the phase 3 trials. Novo Nordisk will be complying to this request by use of the currently available validated neutralization assays.

Does the Agency have any comments to the strategy for analysis of neutralising antibodies in the phase 3 trials?

FDA Pre-Meeting Response

The evaluation strategy of immunogenicity samples obtained during the phase 3 studies is reasonable. The proposed strategy to use a validated, improved neutralizing antibody assay that uses a new positive control to screen samples collected during treatment and follow up is acceptable.

Additional comments:

Provide the validation of the assay employed to test the immunogenicity of samples from the pivotal trial together with the NDA package within the Integrated Summary of Immunogenicity. Provide details on each dilution step during ADA testing and titer determination. Please provide a sortable table that identifies each individual patient and sample that screened postive for ADA. For each sample that screened positive, provide the confirmed ADA positivity status. For samples that are confirmed positive, provide data on titer, neutralizing activity and cross reactivity to the native GLP-1 sequence.

In addition, include a clinical assessment of immunogenicity that links the ADA status and titers with PK, PD, efficacy and safety. The evaluation should also include, but is not limited to, the following information:

	Anti-semaglutide Abs		Persistent Abs		Abs cross-reactive to native GLP-1		Neutralizing Abs	
	yes	no	yes	no	yes	no	yes	no
Mean weight change								
Mean HbA1c change (STEP 2)								
Hypersensitivity AEs, n (%)								
Injection site AEs, n (%)								
Hypoglycemia AEs, n (%)								

For each patient that seroconverts or has a 4-fold increase in titer, provide a graphic representation of their ADA status and relevant PK/PD and clinical measurements over time.

2.2. Regulatory

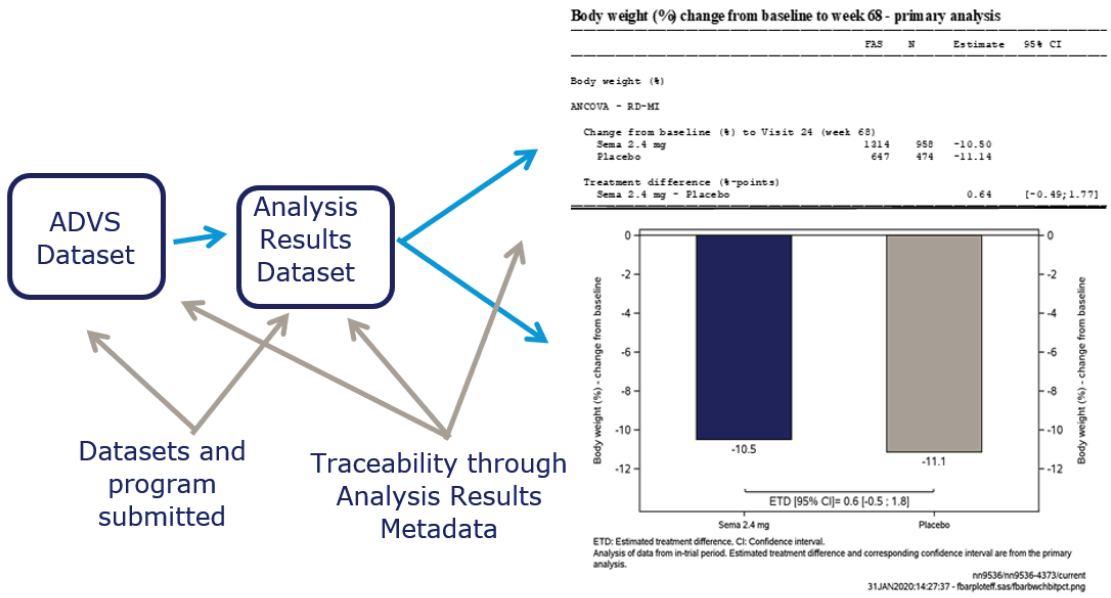
Questions 8 and 9

All trials included in the NDA will be submitted in the CDISC format. SDTM datasets will be provided by trial for all trials and accompanied by a study data reviewer's guide (SDRG), define-xml for SDTM and an annotated CRF. ADaM datasets as well as statistical analysis datasets (AXxx) will be provided by trial for all trials in Table 11-1. This will be accompanied by an analysis data reviewer's guide (ADRG), define-xml for ADaM and the programs that were used to generate the ADaM datasets and statistical analysis programs for primary and confirmatory secondary efficacy endpoints. Statistical analysis programs for subgroup analyses of the primary endpoint will also be submitted. Define-xml for ADaM will include analysis results metadata for end-of-text outputs displaying the results of these analyses. Metadata datasets used for the ADaM and output generation will be provided and submitted in the misc folder of the Module 5 structure in the NDA.

Results from the statistical analyses such as estimated treatment contrasts with associated confidence intervals and p-values are stored in sponsor-defined analysis results datasets. This is done to improve traceability and ensures that statistical analysis results can be displayed in multiple tables, listings and figures without having to redo the calculation of the displayed analysis results, as illustrated in Figure 11-1. This approach reduces the risk of errors.

The analysis results datasets and programs that produce these datasets will be provided to the Agency as part of the NDA and documented in the ADRG and the define-xml for ADaM. The programs that display the results in tables and figures using e.g. proc report or sgplot will not be submitted but can be provided upon request. Analysis results metadata will be included in the define-xml in the format recommended by CDISC in the document Analysis Results Metadata (ARM) v1.0 for Define-XML v2.0. The analysis results metadata will specify the programming statements and selection criteria needed to re-create individual tables, listings, and figures.

Figure 11-1 Traceability through analysis results datasets



Integrated database

An integrated ADaM database will be provided as part of the NDA. This will support the generation of end-of-text output for the integrated summary of efficacy and safety documents. The database will be accompanied by an ADRG, define-xml for ADaM and the programs used to create the integrated database from the trial datasets, as well as a sample programme producing an adverse event overview table based on the integrated database. This programme is included to illustrate how percentages of subjects and adverse event rates are adjusted using the Cochran-Mantel-Haenszel method for all presentations of adverse event data based on the integrated database.

BIMO

Novo Nordisk is planning to provide BIMO (Bioresearch Monitoring) OSI site-level datasets for the phase 2 and 3 trials as SAS transport (XPORT) files accompanied by a separate define.pdf and located in the appropriate Module 5 datasets folder. This is in accordance with the following guidance in the BIMO guide, Section 8:13:

"This by-subject, by-clinical site listing(s) should contain primary and key secondary efficacy parameters or events. For derived or calculated endpoints, the raw data points used to generate the derived or calculated endpoint should be provided."

Sample

Enclosed in Module 5 are sample datasets and Reviewer's Guide. The datasets include a sub-selection of subjects in ADSL and the subjects' full data for selected datasets including the associated define.xml and excerpts from Analysis Data Reviewer's Guide. Data samples are from STEP 1.

The formats in which SDTM and ADAM are provided are displayed in Table 11-1. As has been done for previous NDA filings, Novo Nordisk would like to have a teleconference with the Division soon after NDA filing to orient the reviewers to the datasets.

Table 11-1 SDTM and ADAM formats

Study ID	Phase	Exchange Standards	Terminology standards
NN9536-4590	Phase 1	SDTM v1.4 SDTM IG v3.2 SDTM define xml v2.0 ADaM v2.1 ADaM IG v1.1 ADaM define xml v2.0	MedDRA v22.1 WHODDE Global/B3 1Sept. 2019 SDTM Terminology 2019-12-20 Pinnacle 21 software version 2.2.0 Novo Nordisk configuration file: SDTM-3.2-FDA-ocv2.2.0 xml. (Standard configuration file: SDTM 3.2 xml)
NN9535-4588	Phase 1	SDTM v1.4 SDTM IG v3.2 SDTM define xml v2.0 ADaM v2.1 ADaM IG v1.1 ADaM define xml v2.0	MedDRA v22.1 WHODDE Global/B3 1Sept. 2019 SDTM Terminology 2019-12-20 Pinnacle 21 software version 2.2.0 Novo Nordisk configuration file: SDTM-3.2-FDA-ocv2.2.0 xml. (Standard configuration file: SDTM 3.2 xml)
NN9536-4455	Phase 1	SDTM v1.4 SDTM IG v3.2 SDTM define xml v2.0 ADaM v2.1 ADaM IG v1.1 ADaM define xml v2.0	MedDRA v22.1 WHODDE Global/B3 1Sept. 2019 SDTM CT 2018-09-28 Pinnacle 21 software version 2.2.0 Novo Nordisk configuration file: SDTM-3.2-FDA-ocv2.2.0 xml. (Standard configuration file: SDTM 3.2 xml)
NN9536-4153	Phase 2	SDTM v1.3 SDTM IG v3.1.3 SDTM define xml v2.0 ADaM v2.1 ADaM IG v1.1 ADaM define xml v2.0	MedDRA v19.1 WHODDE 1 September 2016 SDTM Terminology 2018-06-29 Novo Nordisk configuration file: SDTM-3.1.3-FDA-ocv2.2.0 xml. (Standard configuration file: SDTM 3.1.3 xml)
NN9536-4373	Phase 3	SDTM v1.4 SDTM IG v3.2 SDTM define xml v2.0 ADaM v2.1 ADaM IG V1.1 ADaM Define xml v2.0	MedDRA version 22.1 WHODDE Global/B3 1Sept. 2019 SDTM Terminology 2019-12-20 Pinnacle 21 software version 2.2.0 Novo Nordisk configuration file: SDTM-3.2-FDA-ocv2.2.0 xml. (Standard configuration file: SDTM 3.2 xml)
NN9536-4374	Phase 3	SDTM v1.4 SDTM IG v3.2 SDTM define xml v2.0 ADaM v2.1 ADaM IG V1.1 ADaM Define xml v2.0	MedDRA version 22.1 WHODDE Global/B3 1Sept. 2019 SDTM Terminology 2019-12-20 Pinnacle 21 software version 2.2.0 Novo Nordisk configuration file: SDTM-3.2-FDA-ocv2.2.0 xml. (Standard configuration file: SDTM 3.2 xml)

Does the Agency agree that Novo Nordisk provides the raw data points used to generate the derived or calculated endpoints only for the primary and secondary confirmatory endpoints?

FDA Pre-Meeting Response

Yes, your proposal appears acceptable. However, we may request additional datasets or programs if needed during the review process.

Does the Agency agree to the format of the sample datasets, Reviewer's Guide and Define-xml provided?

FDA Pre-Meeting Response

Yes, your proposal appears acceptable.

Question 10

Novo Nordisk proposes to split the Integrated Summary of Safety (ISS) between Module 2 and Module 5 as illustrated in Example 4 in the FDA guidance document: '*Guidance for Industry - Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document'* and in Figure 11-2.

The text portion of the ISS, which is proposed to be placed in Module 2 (Section 2.7.4), is expected to be ~350 pages (with incorporated tables and figures). This is within the typical suggested size limitation for the Summary of Clinical Safety section. The text part of the ISS will include an Executive Summary of Safety to provide an overview of the safety results and safety profile obtained in the phase 3a program. The appendices and datasets will be placed in Module 5 (Section 5.3.5.3). The text in Module 2 (Section 2.7.4) will contain hyperlinks to specific supporting tables/appendices in Module 5 (section 5.3.5.3).

Figure 11-2 Illustration of the ISS split between Module 2 and Module 5.

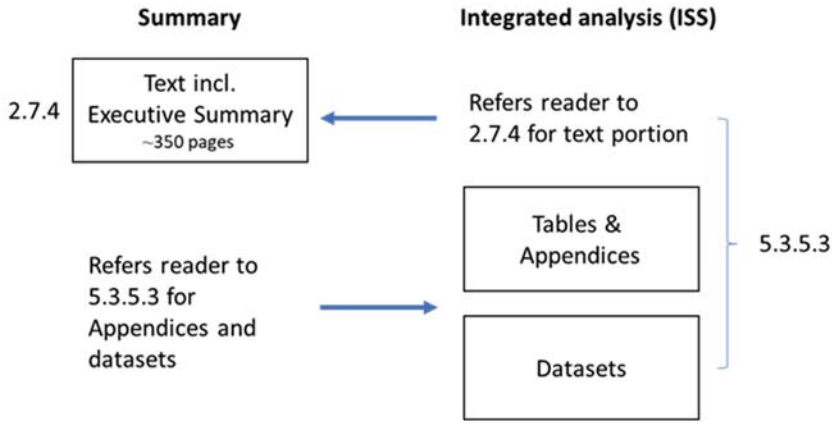


Figure revised from Guidance for Industry - Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document

The ISS including the Executive Summary of Safety will be prepared as it was done for oral semaglutide for T2D (Rybelsus®, NDA 213051). A similar strategy was used for the Summary of Clinical Efficacy and Integrated Summary of Efficacy for oral semaglutide for T2D (Rybelsus®, NDA 213051) and semaglutide s.c. for T2D (Ozempic®, NDA 209637).

Semaglutide is an approved drug with a well-known safety profile, which allows for the text portion of the ISS to be of an appropriate size to also serve as the Summary of Clinical Safety. Flags will be included in the data sets as done for oral semaglutide for T2D (Rybelsus®, NDA 213051) to allow for other safety evaluations, if needed, e.g. specific treatment groups or the total population exposed to semaglutide s.c.

Does the Agency agree with the proposal for the text portion of the Integrated Summary of Safety to function as the Summary of Clinical Safety in Module 2.7.4?

FDA Pre-Meeting Response

Yes, your proposal is acceptable. Ensure links within the SCS allow for reference to the data within the ISS.

Question 11

Novo Nordisk proposes to make all literature references available immediately upon request and not include them in Module 4.3 or Module 5.4 as all literature references are publicly available.

This should comply with M4E(R2): The CTD – Efficacy Guidance for Industry,8 which states that: “Copies of references that are not included here should be available immediately on request”.

Does the Agency agree with the proposal of making the literature references available upon request?

FDA Pre-Meeting Response

Your proposal is acceptable. Please include the PubMed ID with each reference listed.

Question 12

Novo Nordisk will submit the updated semaglutide risk management plan (RMP) to EMA according to EMA requirements. The RMP is compliant with the EMA guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2).15 In accordance with GVP, the aim of the RMP is to document the risk management system considered necessary to identify, characterise and minimise a medicinal product’s important risks. The RMP will cover semaglutide s.c. once weekly for T2D (Ozempic®, NDA 209637), oral semaglutide for T2D (Rybelsus®, NDA 213051) as well as semaglutide s.c. 2.4 mg once weekly for weight management.

For previous NDA filings, Novo Nordisk has included a copy of the EMA RMP in the NDA. However, as the RMP is a document required by EMA, Novo Nordisk proposes to not include the RMP in the NDA.

Does the Agency agree to the proposal of not including a copy of the semaglutide risk management plan in the NDA?

FDA Pre-Meeting Response

No, we do not agree. This document covers the risks of semaglutide, and it is helpful to review it along with the NDA. Please submit your risk management plan in the NDA submission.

Question 13

As previously discussed with the Agency (type C guidance, IND 126360, 04 July 2018, written response received 19 September 2018), Novo Nordisk intends to launch semaglutide s.c. 2.4 mg with the single dose pen-injector (also referred to as DV3396 pen-injector). The single-dose pen- injector is a customized version of the (b) (4) (b) (4) auto-injector, which is a well-established and characterized device, currently used with several approved drug products such as Zembrace® Symtouch® (acute migraine therapy), Benlysta® (monoclonal antibody therapy for systemic lupus erythematosus), Brenzys®/Benepali® (monoclonal antibody therapy for rheumatoid arthritis and certain other autoimmune disorders).

As agreed with the Agency on 04 February 2019, the single-dose pen-injector will also be included in two post-approval clinical trials (one pediatric trial [4512] and one adult [trial 4576]). In order to bridge to the PDS290 pen-injector used in the phase 3a program, Novo Nordisk is conducting two bioequivalence trials between the to-be marketed single-dose pen-injector and the PDS290 pen- injector; trials 4590 and NN9535-4588 (both trials have randomised 68 subjects). The bioequivalence trials will also support the change in formulation between formulation used in phase 3 and the to-be-marketed formulation. The results from the two bioequivalence trials will be included in the original NDA. For more information about the two bioequivalence trials, see Clinical Supporting Documentation, Section 1.5.

Novo Nordisk will also include results from the human factors study in the NDA in support of differentiation and handling of the single-dose pen-injector. The study is planned to enroll 120 subjects and is conducted according to feedback received from the Agency on 17 March 2020.

Novo Nordisk will provide Module 3 documentation to support the single-dose pen-injector and formulation. The Module 3 documents will include documentation of the Essential Performance Requirements and also documentation on the 21 CFR 820 requirements. In addition, Novo Nordisk has worked to incorporate learnings from the recent somapacitan FDA review (BLA 761156).

For more information on the device and formulation, see CMC Supporting Documentation.

Samples of the single-dose pen-injector and carton labelling will be available for the Agency during the NDA review.

Does the Agency have any further feedback on the documentation that will be provided in the NDA to support the single-dose pen-injector?

FDA Pre-Meeting Response

CMC

Regarding the proposed Module 3 documentation for the single-dose pen-injector and formulation, we have the following additional comments:

At the time of NDA submission, provide analytical comparability data for the Phase 3a drug product and the to-be-marketed finished product. In your submission, include full analytical comparison data, including the following:

a) in vitro biological activity comparison for the investigational drug product and to-be-marketed using a cell-based assay

b) oligomerization profile comparison between the Phase 3a investigational product and the to-be-marketed product

c) degradation profile comparison between the to-be-marketed product and the Phase 3 a drug product stored under long-term, accelerated stability and stress stability conditions using appropriate analytical techniques.

Ensure that the application includes justification of the drug product specification acceptance criteria based on data obtained from lots used in non-clinical and/or clinical studies. The acceptability of the proposed comparability protocol will be review issue. For additional information, see the FDA "Guidance for Industry: Changes to an Approved NDA or ANDA" (April 2004) and "Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information" (Draft – Revision 1, April 2016). Additionally, your proposal includes a bracketing approach for process validation across multiple manufacturing facilities. FDA does not approve process validation approaches, protocols, or number of specific batches used in process validation studies. However, it is expected that the validation should sufficiently demonstrate adequacy of manufacturing process at each site of manufacture. Validation protocols, acceptance criteria, and study outcomes (as applicable) may be evaluated during a pre-approval inspection of the manufacturing facilities. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product.

For additional information, refer to FDA's guidance on process validation, "Guidance for Industry Process Validation: General Principles and Practices" (January 2011).

Meeting Discussion

The sponsor clarified their plans to provide data for long-term stability, accelerated stability and stress stability conditions, comparing phase 3 study drug product to the to-be-marketed product (see sponsor slide #2) according to ICH.

FDA responded that the plans appear reasonable. In addition, the sponsor could provide temperature cycling data and stress testing at 40^0. Shorter testing times are acceptable at higher temperatures, such as 50^0.

The sponsor asked if long-term stability data at 37^0 could be provided instead of 40^0. FDA stated this would be acceptable since the goal was to compare the degradation profiles between the study drug product and the to-be-marketed product.

Device

Your design requirement did not cover all aspects of the injector, such as cap removal and needle shielding/lockout (to prevent sharps injury).

Ensure design verification covers all pre-conditioning recommended in ISO 11608-1:2014 Needle-based injection systems for medical use — Requirements and test methods — Part 1: Needle-based injection systems.

The control strategy provided appears incomplete and too high level to determine adequacy. At this time, we do not agree with your proposal of not including activation force, injection time and needle extension into the release specification. (b) (4) controls on components or sub-assemblies will not ensure the injector is adequately controlled without additional information regarding the supply chain, validation reports, and more thorough analysis of all components impacting the EPR.

Please also note that when validating activation force and injection time EPRs your evidence should demonstrate that the limits of the specification, not nominal, are validated.

Meeting Discussion

The sponsor stated they had defined essential performance and safety characteristics of the device. They understood the need for additional details and these will be included in the NDA. They asked for clarification of the pre-meeting statement, *"validating activation force and injection time EPRs your evidence should demonstrate that the limits of the specification, not nominal, are validated"* and asked if this referred to human factors related data.

FDA responded that this was not a human factors request but rather it referred to validating and justifying the limit of the injection time and activation force. These data might be included in a human factors study if the specification limits are used in the study or injection time could be demonstrated in a hold-time study.

Human Factors

From a human factors perspective, your proposal appears reasonable; however, the adequacy of the data that you submit in your NDA will be a review issue. Please refer to our draft guidance titled *Contents of a Complete Submission for Threshold Analyses*

and Human Factors Submissions to Drug and Biologic Applications[1] for the content of a human factors validation study report submission. Human Factors study results should be placed in eCTD section 5.3.5.4 – Other Study reports and related information.

Clinical Pharmacology

In addition to the results from bioequivalence studies 4590 and NN9535-4588, submit the population pharmacokinetic and exposure-response analysis of phase 3 studies STEP 1 and STEP 2.

Question 14

Novo Nordisk acknowledges that final decisions on label text will not be discussed until the NDA is under review. However, Novo Nordisk would appreciate having an early dialog with the Agency at the pre-NDA meeting around the potential requirement for language in the Physician Insert (b) (4)

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

(b) (4)

Acknowledging the final decision on label text will not be discussed until the NDA review, does the Agency have any preliminary feedback on the above proposal?

FDA Pre-Meeting Response

We do not have feedback on your proposal at this time. We will take your comments into consideration during NDA review. Nevertheless, it appears reasonable for you to submit these data to support the proposed labeling, given the reported response rates and extensive pre-market safety information.

Question 15

Novo Nordisk acknowledges that final decisions on label text will not be discussed until the NDA is under review. However, Novo Nordisk would appreciate having an early dialog with the Agency at the pre-NDA meeting around the proposal for the indication text that will be included in the Physician Insert.

(b) (4)

Novo Nordisk proposes the indication as:

TRADENAME is indicated as an adjunct to a reduced calorie meal plan and increased physical activity for chronic weight management (weight loss and weight maintenance) in adult patients with an initial body mass index (BMI) of

- 30 kg/m^2 or greater (obesity), or
- 27 kg/m^2 or greater (excess weight) in the presence of at least one weight-related comorbid condition

Acknowledging the final decision on label text will not be discussed until the NDA review, does the Agency have any preliminary feedback on the proposed indication?

FDA Pre-Meeting Response

Your proposed indication is consistent with the indication of other approved obesity drugs and in general appears reasonable. Specific language, (b) (4) (b) (4) will be determined during NDA review.

2.3. Additional FDA Comments

Clinical:

1. Please include a table of adverse events that include all AEs, not just the ones that occur at a certain percent of subjects.
2. Provide a table of contents for narratives for each trial with active hyperlinks, organizing the listing as described in Section 5.1.3.6 of the Clinical Supporting Documentation, with subcategorization by treatment group.
3. At NDA submission, provide the minutes of all DSMB and steering committee meetings.
4. Include a chronology of prior substantive communications with FDA and copies of official meeting/teleconference minutes.
5. For patients listed as discontinued due to “investigator decision,” “sponsor request, “withdrew consent,” “other,” or similar reasons, the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.
6. Laboratory values from narratives should be included in your submitted datasets. If a reviewer wanted to independently tabulate peak ALT or creatinine values, for example, this should be possible from using the laboratory dataset alone (e.g., LB.xpt) as opposed to some values only appearing in a narrative describing results obtained during a hospitalization. Where laboratory values were obtained should be flagged in the dataset (e.g., routine versus from an adverse event narrative).

Meeting Discussion

The sponsor offered to arrange a teleconference shortly after the NDA submission to walk through the NDA structure and datasets. FDA responded it would be helpful.

Regarding laboratory values, the sponsor stated that the narratives would include central and local laboratory data, similar to what was submitted for Saxenda. Local lab data would be flagged in the laboratory dataset for adverse events within safety focus areas (b) (4).

FDA agreed with the sponsor's proposal.

Regarding the sponsor's identification of renal events in the T2D trial as a safety focus area (b) (4), FDA clarified that renal adverse events in general, not only in patients with T2D, were of interest, given the safety concern for acute renal injury due to gastrointestinal losses and subsequent volume depletion.

7. Please include important regulatory actions in other countries or important information contained in foreign labeling.
8. Include a discussion of the applicability of foreign data to the safety and efficacy of semaglutide in the U.S.
9. Provide the following analyses for laboratory values and vital signs:
    a. Measures of central tendency; provide normal ranges.
    b. Clinically significant and marked outliers; provide criteria used to identify outliers.
    c. Shifts from normal to abnormal.
    d. If there is a signal for abnormal laboratory or vital sign changes, please provide an analysis of persistence of the change (for example, percentage of individuals with 2 consecutive values > x or change in these parameters over time in the individuals that experienced the elevations).
    e. For tables displaying liver enzyme abnormalities, please include a row for potential "Hy's Law" cases (ALT or AST >3x upper limit of normal AND TBL> 2xULN)
    f. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in a SOC pertaining to the specific abnormality, with the abnormal laboratory or vital sign value that triggered the AE.
    g. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
10. Provide overdose experience.

11. Conduct explorations of:

    a. Dose dependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.

    b. Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.

    c. Drug-demographic interactions

    d. Drug-disease interactions

    e. Drug-drug interactions

Device content for marketing application:

Device information should be located in the appropriate eCTD module, as recommended in the FDA's eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" (https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf).
When submitting a marketing application for the final finished combination product, provide the following information related to your device:

1) Device Description Documentation

    a) Provide a description of your device constituent design, including any novel features and/or functionalities. This should include drawings / diagrams of the device, descriptions of device components, or any other available information to explain the device design.

    b) Describe the principles of operation of your device.

    c) Describe any accessories or other devices labeled for use with your device (e.g., co-packaged needle).

2) Design Control (21 CFR 820.30) – The application should include design documentation. The use of recognized standards and FDA guidance to inform design and testing is recommended, as applicable. For questions about design control documentation, we recommend that you reference the FDA Design Control Guidance for Medical Device Manufacturers, https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm070642.pdf. We recommend that the design control information provided in your application include the following:

    a) Design Input Requirements (e.g., safety, performance, and reliability requirements of a device that are used as a basis for device design)

b) Design Output Specifications (e.g., device description, drawings, specifications, bill of materials, etc.)

c) Design Verification Plan/Summary Report, supporting data and traceability

d) Design Validation Plan/Summary Report, supporting data and traceability

e) Risk Management File

3) Essential Performance – Identify essential performance requirements (EPR) for the device.

For each identified essential performance requirement, your marketing application should include verification and validation information of EPR specifications. While the final set of essential performance requirements should be based on your design control process, we are providing the following example EPRs for your device type. This is not an exhaustive list and product specific factors should influence your EPR selection.

Example single dose pen injector:

- Delivered Volume Accuracy
- Activation Force
- Injection Time
- Extended Needle Length

Please refer to the FDA Guidance titled Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products issued in June 2013 at https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm147095.pdf for more details.

4) Additional testing – Regarding your device constitute type, provide (b) (4) (b) (4) testing compliance to ISO 80369.

5) Stability (ICH Q1) – Your stability program should include endpoints to verify that device essential performance is maintained at expiry. You may exclude certain EPRs from the stability study if you can provide scientific rationale that the excluded EPR is unlikely to change over time.

6) Shipping – Provide documentation for the final finished product to demonstrate that the device EPRs are met after shipping.

7) Control Strategy – Provide a control strategy that ensures that the final finished combination product maintains its essential performance requirements. The control strategy may consist of, but is not limited to, lot release, (b) (4) control of incoming materials, purchasing controls, etc.

8) Quality System – The marketing application should contain a complete summary of your base operating system as described in the FDA guidance titled Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products issued in January 2017, available at https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf

Additional Comments

The sponsor commented that the NDA would probably be submitted in late November or December 2020 and they may use a priority review voucher (PRV). If a PRV was used, the sponsor would plan to submit the phase 3 clinical study reports to the IND prior to submission of the NDA.

The sponsor asked if the Agency thought the application would be discussed at an Advisory Committee meeting (AC). FDA responded that the question was premature and the need for an AC would be determined during the review.

3.0 Other Important Information

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[6] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

[6] https://www.fda.gov/media/84223/download

[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

6.0 ATTACHMENTS AND HANDOUTS

4 Pages have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN M SHARRETTS
09/04/2020 12:14:04 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 126360

MEETING MINUTES

Novo Nordisk Inc.
Attention: Stephanie DeChiaro
Director, Regulatory Affairs
P.O. Box 846
800 Scudders Mill Rd.
Plainsboro, NJ 08536

Dear Ms. DeChiaro:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for semaglutide injection.

We also refer to the meeting between representatives of your firm and the FDA on October 23, 2017. The purpose of the meeting was to discuss phase 3 development of semaglutide for chronic weight management.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

James P. Smith, M.D., M.S.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	October 23, 2017; 2:00 – 3:30 PM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	126360
Product Name:	semaglutide injection
Indication:	chronic weight management
Sponsor/Applicant Name:	Novo Nordisk Inc.
Meeting Chair:	James P. Smith, MD, MS
Meeting Recorder:	Patricia Madara, MS

FDA Attendees

Office of the Commissioner (OC); Office of Special Medical Programs (OSMP); Office of Combination Products

Patricia Y. Love, M.D., MBA	Deputy Director (called-in)

Office of New Drugs (OND); Clinical Outcomes Assessment (COA) Staff

Wen-Hung Chen, Ph.D.	Social Science Analyst

OND; Office of Drug Evaluation II (ODE II)

Mary T. Thanh Hai, M.D.	Deputy Director

OND; ODE II; Division of Metabolism and Endocrinology Products

James P. Smith, M.D., M.S.	Deputy Director
Julie Golden, M.D.	Medical Officer
Todd Bourcier, Ph.D.	Pharmacology/Toxicology Team Leader
Fred Alavi, Ph.D.	Pharmacology/Toxicology Reviewer
Julie Van der Waag, MPH	Chief, Project Management Staff
Patricia Madara, M.S.	Regulatory Project Manager

Office of Translational Sciences (OTS); Office of Clinical Pharmacology; Division of Clinical Pharmacology II

Jaya Vaidyanathan, Ph.D.	Clinical Pharmacology Team Leader
Shalini W.S. Yapa, Ph.D.	Clinical Pharmacology Reviewer

OTS; Office of Biostatistics; Division of Biometrics II

Greg Levin, Ph.D.	Team Leader
Roberto Crackle, Ph.D.	Statistical Reviewer

Center for Device Evaluation and Radiological Health; Office of Device Evaluation; General Hospital Devices Branch

Kathleen Fitzgerald	Device Reviewer

Sponsor Attendees

Anne Phillips	Senior Vice President, Clinical, Medical and Regulatory Affairs, US
Charlotte Giwercman Carson	Senior International Medical Manager, Obesity Medical and Science
Christian Foged	Corporate Project Vice President, Obesity
Devraj Chakravarty	Senior Manager, US Regulatory Affairs
Hanne Aae Theilgaard	Senior Global Regulatory Lead, Saxenda and Obesity Projects
Henrik Kim Nielsen	Corporate Vice President, Regulatory Affairs, GLP-1, Obesity & Diabetes Complications
Lars Endahl Statistical	Vice President, Biostatistics & Clinical Reporting
Lisbeth Vestergård Jacobsen	Senior Clinical Pharmacology Advisor, Clinical Pharmacology
Marianne Ølholm Larsen Grønning	Project Vice President, Obesity
Ole Kim Eskerod	Vice President, Obesity Medical and Science
Robert Clark	Vice President, US Regulatory Affairs
Søren Mikkelsen	Corporate Vice President, Device Development
Stephanie DeChiaro	Director, US Regulatory Affairs

1.0 Background

Semaglutide (NN9536) is a long-acting GLP-1 receptor agonist originally studied as an adjunct to diet and exercise for the treatment of type 2 DM (IND 79754). The semaglutide phase 3 program for treatment of type 2 DM is complete and the NDA is currently under review. IND 126360 was opened in June 2015, with submission of a phase 2, placebo-controlled, 52-week, dose-finding study of semaglutide for chronic weight management (Trial 4153). Dosages in this study ranged from 0.05 mg/day to 0.4 mg/day by subcutaneous injection in obese subjects without T2DM. Based on the results of multiple phase 3 studies conducted for the T2DM program under IND 79754, the sponsor proposes once-weekly dosing of semaglutide for obesity

in phase 3. The proposed dosages for the treatment of T2DM are 0.5 mg and 1.0 mg weekly, and the proposed dosage for weight management is 2.4 mg weekly.

On August 4, 2017, Novo Nordisk submitted an end-of-phase 2 meeting request, seeking guidance on the phase 3 development of semaglutide for chronic weight management. The request was granted and the discussion was held on October 23, 2017.

On October 23, 2017, prior to the meeting, the sponsor provided an agenda and additional information related to specific questions / FDA responses that required further discussion.

2.0 Discussion

Sponsor questions and FDA pre-meeting responses follow in regular font. Meeting discussion is in **bold** font.

2.1. Nonclinical

Question 1

Does the Agency agree that cross-referencing to the nonclinical package for the type 2 diabetes (T2D) indication is adequate and sufficient to support initiation of clinical phase 3 development and later submission for the weight management indication?

FDA Pre-meeting Response

Yes. The nonclinical safety assessment you have conducted for semaglutide for diabetes indication will support initiation of phase 3 studies and a future NDA submission for obesity indication.

Discussion

No additional discussion.

2.2. Abuse Dependence

Question 2

Based on the nonclinical and clinical rationales provided, does the Agency agree that no dedicated nonclinical abuse/dependence potential studies are required to support the NDA filing of a weight management indication and that it is sufficient to cross-refer to the nonclinical safety pharmacology studies in the semaglutide s.c. NDA for the T2D indication?

FDA Pre-meeting Response (sent by email on October 23, 2017)

We agree. Nonclinical abuse-related studies are not recommended at this time.

Discussion

No additional discussion.

2.3. Clinical

Question 3:

The proposed indication for semaglutide s.c. in weight management is: "as an adjunct to a reduced−calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of

- ≥30 kg/m² (obese), or
- ≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes mellitus or dyslipidemia)."

Does the Agency agree that the proposed trials and trial designs, specifically the inclusion/exclusion criteria and endpoints, are adequate to support the proposed indication, under the assumption that the benefit-risk profile is favorable?

FDA Pre-meeting Response

Overall, your proposal that includes four 68-week trials (including dose escalation) in a population of patients with BMI ≥30 kg/m², or ≥27 kg/m² in the presence of at least one weight-related co-morbidity, is consistent with the weight management guidance and would be supportive of the proposed indication. We have some comments for you to consider:

a. Although we acknowledge many of the proposed exclusions have been used in previous trials, too stringent an approach can limit the safety evaluation, particularly for an obesity drug. Given the growing experience with GLP-1 agonists for type 2 diabetes and obesity, it would be reasonable to consider loosening some of these eligibility restrictions (e.g., history of pancreatitis; MI, stroke unstable angina, or TIA within 180 days; major depressive disorder within 2 years; PHQ-9 ≥ 15, lifetime history of a suicidal attempt) in order to broaden and generalize the patient population.

b. Please clarify the objective of the phase 3b trial. Are you proposing to submit this trial for review post-approval? Are you anticipating any additional indications based on this trial? While we acknowledge the advantages of a longer-term assessment of safety, a database of 150 patients randomized to drug for this 2-year trial seems inadequate for a safety evaluation. We are interested in exploring with you the feasibility of conducting an outcomes trial to assess long-term benefit of semaglutide in patients who are at high risk for morbidity or mortality from their obesity (based on BMI, age, and/or co-morbid disease). Endpoints could include adjudicated MACE, but others as well, such as pre-specified deaths and hospitalizations that are considered likely related to obesity.

Discussion

The sponsor asked for additional clarity on the recommendations to loosen exclusion criteria. FDA noted these examples were intended to encourage enrollment of a more "real-world" patient population and perhaps avoid some of the limitations that have been placed on labels for other drugs, particularly given the experience with semaglutide specifically, but also the GLP-1 class more generally, for both diabetes and obesity. For example, enrolling certain patients with a history of pancreatitis could be considered, given the experience with enrolling some of these patients in the LEADER trial.

The sponsor agreed but stated that it could be difficult to get some investigators to enroll higher-risk patients. The Agency acknowledged the challenges but encouraged the sponsor to consider patients who would be likely to use the drug, if approved, and not to be excessively concerned that small imbalances in certain safety parameters that might result from baseline comorbidities would be a major impediment in the drug's development.

The sponsor provided clarification regarding their proposed phase 3B trial. This two-year study would be submitted as a post-approval supplement, and they would not be seeking a new indication. They noted that it was designed to address a limitation of use in the EU label.

Question 4:

Does the Agency agree that the number of subjects and the extent of exposure are sufficient to pursue the proposed weight management indication, under the assumption that the benefit-risk profile is favorable?

FDA Pre-meeting Response

We agree. See additional comments in the response to question 3.

Discussion

No additional discussion.

Question 5:

For CV safety, Novo Nordisk proposes to fully cross-reference the cardiovascular (CV) outcome trial conducted for the semaglutide s.c. T2D clinical development programme. Does the Agency agree that this approach is adequate to support the weight management indication?

FDA Pre-meeting Response

We agree, assuming that no unanticipated CV safety concerns are identified during review of the weight management phase 3 program. Note that although we are not asking you to prespecify a noninferiority margin for an unacceptable increase in CV risk, the evaluation of the effect of semaglutide on CV risk in patients treated for weight management will be an important review issue. This evaluation will be informed by both the CV outcomes data in T2D as well as the data related to CV events in your weight management program. Therefore, you should estimate the expected number of MACE events in your phase 3 weight management program and justify that the evaluation will provide reasonable precision around the estimated effect on CV risk.

We encourage you to explore the feasibility of an outcomes trial to more fully understand the long-term benefits of semaglutide in patients with obesity. See the response to question 3.

Discussion

The sponsor provided details and clarification related to their cardiovascular safety proposals. The Saxenda phase 3A studies resulted in 0.16 and 0.43 events per 100 patient years for liraglutide and placebo, respectively. Therefore, the sponsor estimates that the event rate in the semaglutide program will be between 0.1 and 0.5 events per 100 person-

years, which should lead to 6 to 30 expected MACE events. Using the higher estimate of the MACE rate of 0.5 (which might be expected if eligibility criteria for the Phase 3 program were loosened) and assuming that a hazard ratio of 1 comparing treatment arms were to be observed, the sponsor estimates an upper-bound of the 95% confidence interval to be approximately 2.1.

FDA noted that the sponsor should pre-specify the statistical analysis plan; FDA and the sponsor agreed that DMEP would review the proposal prior to unblinding.

The sponsor suggested that discussion of an outcomes trial designed to investigate whether semaglutide reduces cardiovascular risk compared with placebo, could occur at a separate type C meeting. FDA agreed and encouraged the sponsor to request such a meeting.

Question 6:

Does the Agency agree that the overall safety profile of semaglutide for weight management can be sufficiently established by the planned safety assessments in the phase 3a trials?

FDA Pre-meeting Response

We note that you are only proposing to obtain fundus photography or dilated fundoscopy at baseline in trial 4374. Given that uncertainty remains regarding the mechanism and long-term risk of diabetic retinopathy among semaglutide-treated patients, we are interested in hearing a proposal regarding how this risk might be investigated further in the weight management program.

We have some safety monitoring proposals for you to consider:

a. Regarding pancreatitis, in addition to accepting or rejecting the diagnosis, consider allowing adjudicators assign a category such as 'likely, but not enough information to confirm'. In previous reviews of liraglutide, pancreatitis was not confirmed in some cases because the strict diagnostic criteria were not met as a result of incomplete data collection.

b. We acknowledge the limitations and burden of adjudicating neoplasms, and we agree with your proposal not to adjudicate all malignancies. However, you should ensure that data collection is comprehensive for malignancies so that informative narratives can be written. In order to better characterize malignancies of interest that arose in the liraglutide reviews, consider obtaining mammograms on all women at baseline and annually (if clinically indicated), and skin examinations in all patients as part of the study physical examinations, to reduce the likelihood of screening biases.

c. Consider obtaining baseline and end-of-study gallbladder ultrasounds in a subset of patients.

d. We note that five women became pregnant while participating in trial 4153. Describe how you plan to ensure women of child-bearing potential will be informed about and adhere to contraception.

e. Finally, we would be open to considering a more simplified safety data collection for certain non-serious adverse events and routine laboratory data not identified as of special interest. See *FDA Guidance for Industry: Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations*.

Discussion

The sponsor clarified their proposed safety monitoring and exclusion criteria. Patients requiring insulin or diagnosed with progressive retinopathy would be excluded. In addition, patients would be monitored for retinopathy using fundus imaging at baseline and week 68. The sponsor plans to collect additional data related to retinopathy.

FDA noted there has not been opportunity for internal discussion of recommendations made at the October 18, 2017, advisory committee meeting that discussed semaglutide for the treatment of type 2 diabetes. In general, however, although panelists acknowledged the possibility that glucose-lowering contributed to the observed increased risk in retinopathy complications, the definitive mechanism remains unknown. Thus, FDA believes that the development of semaglutide for obesity would provide another opportunity to further investigate this risk. If the sponsor pursues a CVOT for semaglutide, this would provide a mechanism for longer-term follow-up; alternatively, the risk could be evaluated in an extension of the weight loss trial for patients with diabetes.

Since the sponsor was proposing to exclude patients with retinopathy, FDA asked whether the sponsor is suggesting that semaglutide should not be used by patients with retinopathy. The sponsor clarified that they were still considering the input of the advisory committee meeting themselves and will discuss possible revision of the protocol.

Regarding pancreatitis, the sponsor commented that they would capture additional data from adjudicators regarding reasons for not confirming events.

Regarding neoplasms and gallbladder events, the sponsor indicated that they would collect more data, including relevant baseline history and risk factors. Mammograms will be obtained at the end of treatment, at the investigator's discretion.

FDA acknowledged that the suggested monitoring using systematic data collection was a recommendation and not a requirement.

Regarding the question of the reported pregnancies in trial 4153, the sponsor clarified that 4 of 5 pregnancies occurred during the seven-week off-drug study period. However, they agreed to improve the informed consent process and emphasize to investigators the importance of contraception, including during the off-drug period.

The company asked FDA to elaborate on their proposal to simplify safety data collection for certain non-serious adverse events and routine laboratory data. FDA explained that given the experience with GLP-1 receptor agonists, a more targeted safety focus might be acceptable. For example, it may not be necessary to submit the typical battery of routine lab data collected for all trial participants. The FDA guidance describes a more streamlined approach to adverse event data collection for certain non-serious AEs. Recognizing that other global regulatory authorities may have their own requirements, the Division suggested that one option to consider would be more rigorous collection of safety data in a pre-specified subset of patients. The sponsor suggested that, in response to FDA's preliminary comments, they were considering reducing or eliminating the routine collection of lipase, amylase, and calcitonin. FDA encouraged the sponsor to submit a protocol for feedback and specifically describe what data collection they propose to reduce or eliminate.

Question 7:

Does the Agency agree to the proposed semaglutide s.c. target dose selection of 2.4 mg/week and dose escalation regimen for the weight management indication, under the assumption that the benefit-risk profile is favorable?

FDA Pre-meeting Response

We note that you are proposing a dose and dosing regimen for Phase 3 that was not evaluated in the Phase 2 dose-ranging trial, which is a risk for any drug development program. While the approach to dose selection may be reasonable, the Agency has not completed review of the population pharmacokinetic modeling and simulation data submitted on 10/11/2017. Additional comments may be provided following review of the submitted data at the time of post-meeting comments. We have the following additional information request to aid in review of the modeling data:

- The modeling is conducted under the assumption that PK is linear in the dose-range evaluated. Provide dose-proportionality data for doses up to 2.4 mg.

We encourage you to consider exploring alternative doses in the phase 3 program. For example, we note that you are anticipating that 17% of patients in trial 4376 will not be able to reach the 2.4 mg target dose. In trial 4376, you could consider randomizing those patients who would have discontinued due to tolerability reasons to either remain on their maximally tolerated dose or withdraw to placebo after the run-in period, to assess whether such patients should remain on a lower dose or discontinue therapy. See additional comments regarding trial 4376 in the response to question 13.

We would be open to proposals that included this concept of a maximally tolerated dose in other trial designs as well, rather than discontinuing all 2.4 mg-intolerant patients from therapy in all trials. We acknowledge that a number of issues would have to be considered and addressed, including blinding and analysis. Proof-of-concept could be tested in trial 4376 as above, and studied further in a larger post-marketing trial (see the response to question 3).

Another study design you may wish to consider in order to explore alternative doses – and to supplement the results of trial 4374 – could be to randomize patients with type 2 diabetes who have been treated with semaglutide 1 mg for glycemic control in a run-in period, to stay on the 1 mg dose vs. escalate to 2.4 mg in a blinded fashion. Key endpoints would be weight-related, but tolerability could be assessed as well.

Discussion

The sponsor responded to the information request above, (b) (4) (b) (4). The sponsor reported that dose proportionality up to a semaglutide dose of 0.4 mg once daily was demonstrated for semaglutide exposure (Cavg). Dose proportionality assessment for Cmax for the doses evaluated in the Phase 2 study was not feasible since sparse sampling was performed in the study. However, dose proportionality for Cmax up to a semaglutide dose of 1.5 mg once weekly was demonstrated in healthy subjects in a study conducted in the T2DM program. Therefore, the sponsor concludes that these data support the assumption of dose proportionality up to a semaglutide dose of 2.4 mg in the PK model. The sponsor will submit a formal response to this question to the IND.

FDA noted that they were still reviewing the PK modelling data and would respond at a future time.

The sponsor noted that they were proposing to keep patients in most of the Phase 3 trials at the patient's maximally tolerated dose (MTD). This is a different treatment approach than was done in the Saxenda studies. For trial 4376 specifically, which is evaluating only those patients who can reach and tolerate the 2.4 mg/week dosage for four weeks, patients will be able to decrease their dose later on if there are tolerability issues.

FDA suggested that a randomization of patients in this trial who do not reach the 2.4 mg dose (to either remain on their maximally tolerate dose or withdraw to placebo) would address an additional question, specifically whether such patients should continue with treatment or be discontinued. The sponsor pointed out that if 15% of subjects cannot reach the 2.4 mg dose, this represents about 150 patients, but one-half may stop treatment for reasons other than tolerability. Information from the 75 remaining patients would not provide enough information for analysis. They suggested this model could be considered for a phase 3B study. FDA pointed out that randomized, controlled data from 75 patients would be better than having no randomized, controlled information, although agreed that the data may be imprecise. Having the data without a control would be difficult to analyze.

The sponsor clarified that the objective of the trial is to quantify the effect of semaglutide at 2.4 mg/week vs. placebo. Those subjects stopping before reaching the 2.4-mg dose would not be integrated; the primary analysis would be from randomization to the end of the trial. In addition, the company explained that a secondary objective could be the rate and extent of weight regain after switching to placebo. The sponsor stated this would provide valuable information. FDA stated that such a trial would require additional consideration upon review of the protocol. For example, the Agency questioned the value of quantifying the rate of weight regain since it is already known that patients gain weight after discontinuing treatments that promote weight loss.

2.4. Statistical

Question 8:

Does the Agency agree with the statistical hierarchical testing procedure (b) (4) (b) (4) to support the weight management indication for semaglutide s.c.?

FDA Pre-meeting Response:

We agree that the hierarchical testing procedure adequately controls the type 1 error probability. However, (b) (4) (b) (4) will be a review issue (b) (4) (b) (4)

Note that if you intend to seek claims in labeling about effects on HbA1c at the dose being developed for weight management, we will need to have further discussions with you and the DMEP diabetes team about how to appropriately evaluate this (b) (4).

Discussion

The sponsor stated they were interested in including data related to T2DM in the semaglutide obesity drug labeling, using the 2.4 mg dose. They asked what would be required, and FDA indicated they could request a Type C meeting for further discussion. The Agency noted that historically, changes in HbA1c were included to show some of the metabolic changes that accompany weight loss. When a drug leads to a reduction in HbA1c regardless of weight loss, however, this presents a different paradigm. FDA is willing, however, to discuss this situation further internally and consider whether there would be a path forward for including HbA1c data in the semaglutide weight management label. Having HbA1c in the hierarchical testing is necessary but not sufficient; at this time, it is unclear what claims would be appropriate for labeling.

Question 9:

Assuming the results are confirmatory, can the data and the p-values from the four domains of the proposed testing hierarchy be included in the clinical studies section of the label?

FDA Pre-meeting Response:

See response to question 8.

Discussion

No additional discussion.

Question10:

Does the Agency agree with the proposed way of handling missing data?

FDA Pre-meeting Response:

Your proposed method of handling missing data appears to be reasonable but sufficient details on your planned multiple imputation approaches should be included in your statistical analysis plan (SAP) such that the results could be replicated based on only the SAP and the data (e.g,, the SAP should pre-specify the exact model, the number of imputations, the random seed(s), etc.).

Discussion

No additional discussion.

Additional Pre-meeting Statistical Comments:

1. For serious adverse events and adverse events of special interest (e.g., your planned safety focus areas), we recommend prospectively planned analyses that compare treatment groups with respect to risk, e.g., with a rate ratio, risk difference, hazard ratio, or relative risk, along with a confidence interval for the chosen metric to help quantify the uncertainty in the treatment comparison (no hypothesis testing is necessary).
2. We appreciate the steps you have taken to prevent missing data and acknowledge the retention rate among subjects who discontinued treatment (64%) was good in trial NN9536-4153. We expect this type of success rate or better in the 4 proposed trials. When developing

your protocols we recommend the following: (1) the only reasons for study withdrawal are loss to follow-up or a patient's withdrawal of consent, with withdrawal of consent meaning that the patient no longer consents to being followed for additional outcome assessments; (2) site investigators are trained about the importance of retention and steps to prevent missing data; (3) the consent forms include a statement educating patients about the continued scientific importance of their data even if they discontinue study treatment early; and (4) several approaches are implemented to retain patients who fail to actively maintain contact with the investigator (e.g., telephone calls to friends or family members, e-mails, offers for transportation to the clinic, etc.).

2.5. Clinical Pharmacology

Question 11:

Novo Nordisk proposes to characterize the clinical pharmacology properties of semaglutide s.c. when used for weight management by population pharmacokinetic and exposure-response analyses based on phase 3a trial data. For further characterization, Novo Nordisk proposes to cross-reference the clinical pharmacology program (including the QTc trial) conducted with semaglutide s.c. for treatment of T2D. Does the Agency agree that this approach is adequate to support the weight management indication?

FDA Pre-meeting Response

Regarding the QTc trial, the proposed cross-referencing approach is adequate to support the weight management indication.

Your approach to characterize the clinical pharmacology properties of semaglutide SC for the weight management program by using population pharmacokinetic and exposure-response analysis based on Phase 3a trials is reasonable. You are planning to obtain PK in studies 4373 and 4374 for population PK analysis. Ensure that you have adequate PK sampling to characterize semaglutide PK and to assess impact of various covariates on PK. Since a higher maintenance dose of 2.4 mg/week is proposed to be administered for the weight management program when compared to the T2DM program, we recommend that you use renal impairment as a covariate in the population PK analysis along with other covariates (e.g., age, gender, body weight, injection site, anti-drug antibodies). Submit to the Agency the modeling analysis plan for review.

We do not agree with your proposal to cross-reference the gastric emptying study for assessment of drug-drug interaction conducted with semaglutide SC for treatment of T2DM. We recommend that you address the effect of 2.4 mg/week semaglutide on gastric emptying.

Discussion

The sponsor reported that they will conduct a study to evaluate gastric emptying using semaglutide 2.4 mg once weekly. The sponsor plans to enroll patients with renal impairment in the Phase 3 trials and agreed to use renal function as a covariate in the population PK model. A modelling analysis plan will be submitted to the Agency for review prior to unblinding.

Question 12:

Based on the rationale provided for the similarity between the intended to-be- marketed semaglutide s.c. drug product concentrations and the phase 3a drug product concentrations; does the Agency agree with the proposal that a bioequivalence trial is not required to support the intended to-be-marketed drug product?

FDA Pre-meeting Response

We strongly recommend that the intended to-be-marketed drug products be used in Phase 3 studies. Provide an explanation as to why the intended to-be-marketed drug products will not be available prior to commencement of the Phase 3 program and the estimated timeline as to when you expect the intended to-be-marketed drug products will be available.

Study NN9535-3687 established bioequivalence between the 1, 3, and 10 mg/mL drug product strengths based on the primary endpoint of AUC0-infinity. However, a trend towards flatter peak concentrations of semaglutide (Cmax) and delay in time to peak concentrations (tmax) was observed with decreasing drug product strengths. These observations may be due to a larger injection volume administered with the lower drug product strength (1 mg/mL) compared to the higher drug product strength (10 mg/mL). The largest injection volume administered in this study was 500 µL. In the weight management program, injection volumes greater than 500 µL will be administered for both the Phase 3 drug product strengths and intended to-be-marketed drug product strengths. Additionally, the injection volumes vary at certain doses between the Phase 3 drug product strengths and intended to-be-marketed drug product strengths (i.e. 1.7 mg/week dose: 570 µL and 750 µL injection volume for the Phase 3 drug product strength (3 mg/mL) and intended to-be-marketed drug product strength (2.27 mg/mL), respectively).

Therefore, despite Study NN9535-3687 establishing a bridge for the drug product strengths, the bridge for injection volume up to 800 µL is lacking. The impact of the higher injection volumes (greater than 500 µL) on the pharmacokinetics of semaglutide is therefore unknown based on this study. Provide justification as to why the pharmacokinetics of semaglutide will not be impacted by different injection volumes. Justify why different efficacy/safety profiles with different injection volumes are not expected when comparing the Phase 3 drug product strengths and intended to-be-marketed drug product strengths. Additionally, clarify what device was used to deliver doses in Study NN9535-3687 and how this device differs to that proposed to be used in the Phase 3 program and intended to-be marketed product for the weight management program. Provide clarification as to whether the (b) (4) manufacturing process for the drug substance is used for all the proposed Phase 3 drug product strengths and intended to-be-marketed drug product strengths.

Discussion

The Agency stated having adequate data from a single-dose bridging study was difficult when there had been so many changes in different trials. Currently, it is unclear whether the phase 3 program could be bridged to the to-be-marketed product. The sponsor stated that they will not have the to-be-marketed drug products ready in time for the Phase 3 program. FDA recommended that the to-be-marketed drug product should be used in at least one of the Phase 3 studies; the sponsor commented that this would be conducted if possible.

The sponsor clarified that the (b) (4) manufacturing process for the drug substance will be used for the drug products for the Phase 3a studies and the to-be-marketed products. They clarified that the device used in Phase 3 studies would be similar to the to-be-marketed pen.

The sponsor stated that for semaglutide the overall systemic exposure is the important PK endpoint, and in Study NN9535-3687, equivalence was demonstrated for semaglutide systemic exposure for all 3 drug product strengths. The sponsor acknowledged that with different injection volumes the Cmax values may change; however, they do not consider the Cmax endpoint to be clinically relevant.

FDA asked the sponsor whether different injection volumes have been associated with different injection site reactions based on their experience in the T2DM program. The sponsor responded that there have been no notable differences in safety with different injection volumes. The sponsor should include any supportive safety information from other programs in the semaglutide obesity submission.

The sponsor stated that in the T2DM program, the injection volume used in the SUSTAIN Phase 3 studies with the 1-mg dose (1.34 mg/mL drug product strength) was 750 µL, and the injection volumes in Phase 1 studies (NN9535-3685, -3684, -3819) in subjects with T2DM and obesity with a 1 mg dose were 340 µL (3 mg/mL drug product strength) and 750 µL (1.34 mg/mL drug product strength). In the Phase 1 studies, the PK of semaglutide was consistent across the different injection volumes. Therefore, they contend that these data support injection volumes up to ~750 µL. The sponsor asked the FDA if such cross-trial data are adequate to support injection volumes of up to 800 µL and 750 µL proposed to be used in the Phase 3 trials and to-be-marketed drug products. FDA responded that the briging data would require review before commenting. The sponsor will submit the bridging data for review.

The sponsor stated that the device used in Study NN9535-3687 was NovoPen 4, which has similar specifications in dose accuracy as the proposed device to be used in the Phase 3a studies and the to-be-marketed drug products.

The sponsor stated that the difference between the drug products used in the Phase 3a studies and to-be-marketed products is (b) (4); the excipients are the same.

2.6. Phase 3a, Trial 4376

Question 13:

Does the Agency agree that an evaluation of the effect, tolerability and safety of semaglutide s.c. in subjects who have reached the target dose in Trial 4376 is of clinical relevance?

FDA Pre-meeting Response

We would like to better understand the objectives of trial 4376. For example, if you are interested in exploring a stopping rule, you should clarify the justification for the run-in duration since 4 weeks on target dose might not be enough time to make a treatment decision. One clinical question of interest from this trial might be the weight results of semaglutide vs. placebo

in patients who are 'non-responders' during the run-in period, i.e., whether patients who do not experience a certain threshold reduction in weight after a reasonable duration of treatment should continue to receive the drug. To address this question, you could consider prospectively planned analyses within strata defined by the amount of weight loss experienced during the run-in. For example, you could plan a regression analysis of the weight change at some time point after randomization as a function of the treatment (remaining on drug versus withdrawing to placebo), the weight change during the run-in period, and the interaction between treatment and run-in weight change. Simultaneous 95% confidence bounds could be determined for the treatment effect as a function of the percent weight loss by the end of the run-in to help inform decisions regarding whether patients with a specific degree of weight change should continue or discontinue semaglutide. You could also consider stratifying randomization by some amount of percent weight loss during the run-in.

Discussion

The sponsor thanked FDA for valuable suggestions (b) (4). They commented they would investigate subgroup analyses based on the amount of weight lost during the run-in and determine if there are differences in the treatment effect across these subgroups.

2.7. Antibody Assessment Strategy

Question 14:

Does the Agency agree with the proposed strategy for sampling, analyzing and reporting of anti−drug antibodies in the confirmatory program for semaglutide s.c. for weight management, and that data of up to one-year on target dose is sufficient for the evaluation of immunogenicity?

FDA Pre-meeting Response

The sampling time points, tiered screening strategy, and reporting the results of the anti-drug antibody analyses at the end of the trial are acceptable. Data of up to one year on target dose seem sufficient for the evaluation of immunogenicity but the final decision will be made after looking at the complete immunogenicity dataset in your NDA submission.

Discussion

No additional discussion.

Question 15:

Due to the high levels of circulating drug during treatment interfering with the cell- based neutralizing antibody assays, does the Agency agree that in vitro neutralizing antibodies are only analyzed after wash-out of drug at follow up?

FDA Pre-meeting Response

No. Assessment of neutralizing antibodies only at the end of the study after the drug wash out period does not capture the incidence and levels of neutralizing antibody during the study and precludes an analysis of whether they have an impact on the safety and efficacy of the product. If possible, you should develop a sensitive assay that allows for testing throughout the study.

Discussion

No additional discussion.

Question 16:

Based on the expectation that the antibody responses in the population with obesity and the population with T2D are similar, and that the %B/T levels are below 60% B/T (which is within the dynamic range of the %B/T dose-response), does the Agency agree that %B/T results can substitute titration of antibody samples below 60%B/T?

FDA Pre-meeting Response

No. Although the RIA is semiquantitative, it is not possible to extrapolate the %B/T to absolute quantities of antibodies since the binding curve of the positive control may be different to that of a polyclonal response to the product. Therefore, titer is the preferred format to relate the levels of ADA induced. All steps of the assay system should be considered when reporting the ADA titers.

Discussion

No additional discussion.

2.8. Additional FDA Pre-meeting Comments

You have stated that the investigational device PDS290 pen-injector combination product for semaglutide 1.34 mg/mL to be used in the phase 3 studies will use the same device portfolio as the to-be-marketed device. You have provided an overview of the pen-injector to be used in the phase 3 clinical trial. For the pen-injector used in the phase 3 trial you will need to demonstrate that the risk of patients selecting the wrong dose is adequately mitigated. In addition, please provide the pen-injector performance data and describe the needles that will be used for the study. For pen-injectors we expect the essential performance requirements to include, at a minimum, the following:

- Dose Accuracy
- Activation Force or Break loose / Glide Force
- Needle Length / Gauge

3.0 Additional Important Information

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized

format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials

used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.

c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

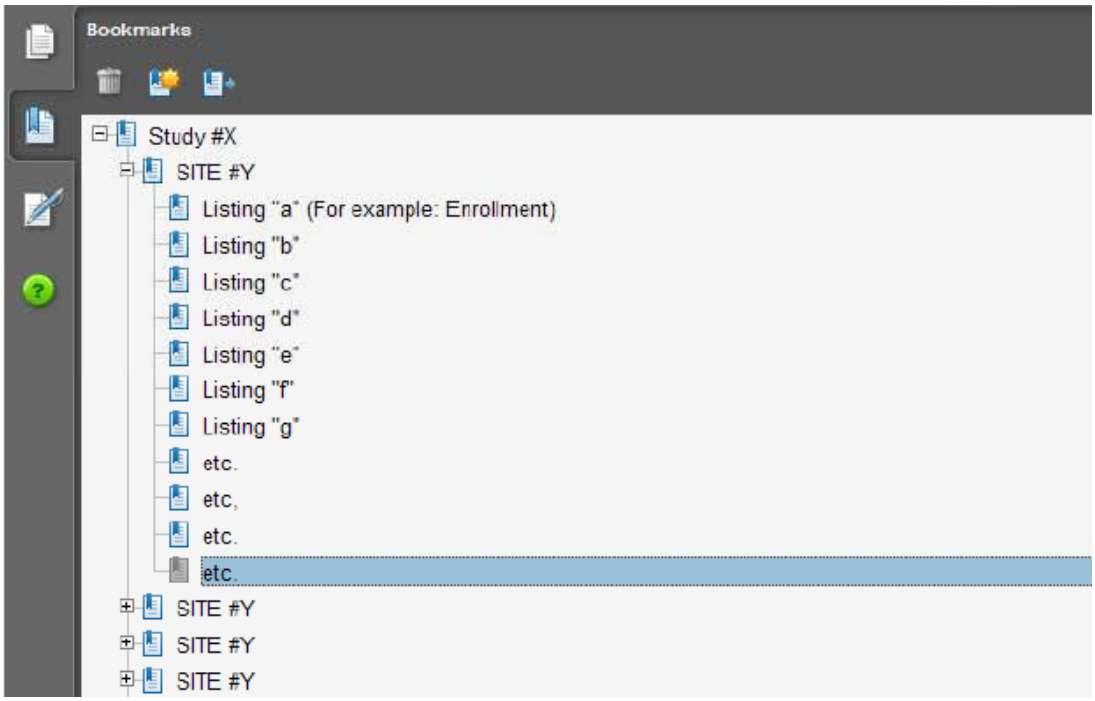
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

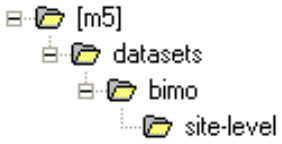
Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

[Insert action item with a brief description, if applicable]	Sponsor	[Insert date]

4.0 ATTACHMENTS AND HANDOUTS

5 Pages have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES P SMITH
11/22/2017